Notice/Disclaimer: The clinical information contained herein is provided for the express purpose of aiding the Pharmacy and Therapeutics ("P&T") Committee members in reviewing medications for inclusion in or exclusion from the Virginia Preferred Drug List. This information is not intended nor should it be used as a substitute for the expertise, skill, and judgment of physicians, pharmacists, or other healthcare professionals. The absence of a warning for any given drug or drug combination should not be construed to indicate that the drug or drug combination is safe, appropriate or effective for any given patient. This information is intended to supplement the knowledge and additional resources available to the P&T Committee members and should not be considered the sole criteria used by the P&T Committee in deciding what medications will be included or excluded from the Virginia Preferred Drug List.

Characteristic	Morphine Sulfate Sustained Release		
	MS Contin®, Oramorph®	Kadian®	Avinza®
Pharmacology	Morphine sulfate is a pure opiate agonist, relatively selective for the mu receptor. Its pharmacological effects include analgesia, drowsiness, changes in mood. respiratory depression, cough suppression, miosis, constipation, nausea and vomiting.		
Date of FDA Approval		July 3, 1996	April 20, 2002
Generic available?	Yes	No	No
Patient Expiration (if single source)		April 13, 2010	November 25, 2017
Manufacturer (if single source)		Alpharma	
Dosage forms / route of admin	Oral tablets – 15, 30, 60, 100 and 200 mg	Oral capsules – 20, 30, 50, 60 and 100 mg	Oral capsules – 30, 60, 90 and 120 mg
Dosing frequency	BID	QD - BID	QD
General dosing guidelines	200 mg tablets recommended for use in opiod-tolerant patients only		Maximum dose = 1600 mg/day (Avinza® doses greater than this contain an amount of fumaric acid that has not been demonstrated to be safe and may result in renal toxicity)
	Dosing regimen should be adjusted for each patient individually, taking into consideration the patient's prior analgesic treatment experience		
	Tablets are to be taken whole, and are not to be broken, chewed, or crushed.	Capsules should be swallowed whole (alternatively, the capsules can be opened and the contents sprinkled on a small amount of applesauce – the beads/pellets should not be crushed, dissolved or chewed)	
Pediatric Labeling	Safety and efficacy not established in children.	Safety and efficacy not established in patients below 18 years of age.	Safety and efficacy not established in patients below 18 years of age.

Characteristic	Morphine Sulfate Sustained Release		
	MS Contin®, Oramorph®	Kadian®	Avinza®
FDA Labeled Indications	Controlled-release oral morphine formulation indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.	Kadian® is indicated for the management of moderate to severe pain where treatment with an opioid analgesic is indicated for more than a few days Kadian® is not recommended as an analgesic for the treatment of acute pain or in the postoperative setting and is not recommended for such use	Avinza capsules are a modified-release formulation of morphine sulfate intended for once daily administration indicated for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. Avinza is not intended for use as a prn analgesic.
Contraindications	Patients with known hypersensitivity to morphine, patients with respiratory depression in the absence of resuscitative equipment, patients with acute or severe bronchial asthma, patients with know or suspected paralytic ileus		
Drug interactions	▪ Drug to drug interactions are pharmacodynamic, not pharmacokinetic (ex. Additive effects with other CNS depressants).		
Major AEs / Warnings	▪ Potential for abuse and/or addiction ▪ Respiratory depression ▪ Constipation ▪ Use with caution in patients with head injury and increased intracranial pressure ▪ Hypotension ▪ GI obstruction ▪ Use with caution in patients with severe renal or hepatic insufficiency, BPH, Addison's disease, hypothyroidism, biliary tract disease elderly or debilitated patients		
Pharmacokinetics issues	Can be administered without regard to food		
Key Populations	• Elderly may be more sensitive to the effects of morphine. • Pregnancy Category: C • Not recommended for use by nursing mothers • Clearance of morphine may be higher in Chinese subjects when compared to Caucasian subjects. • Clearance is decreased with hepatic failure and renal insufficiency		

Characteristic	Morphine Sulfate Sustained Release		
	MS Contin®, Oramorph®	Kadian®	Avinza®
Notes:	MS Contin does not release morphine continuously over the course of a dosing interval. The administration of single doses of MS Contin on a q12h dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations on a q4h regimen.	When given once-daily (every 24 hours) Kadian® had a similar C_{max} and higher C_{min} at steady state in clinical usage, when compared to twice-daily (every 12 hours) controlled-release morphine tablets (MS Contin®), given at an equivalent total daily dosage	Avinza capsules contain two components, an immediate release component and an extended release component that maintains plasma concentrations during the 24 hour dosing interval

Characteristic	Oxycodone Hydrochloride Extended Release	Fentanyl Transdermal
	Oxycontin®	Duragesic®
Pharmacology	Opiate agonists that pharmacological effects include analgesia, drowsiness, changes in mood. respiratory depression, cough suppression, miosis, constipation, nausea and vomiting.	
Date of FDA Approval	December 12, 1995	August 7, 1990
Generic available?	No (multiple generics have received tentative approval)	Generic approved on November 21, 2003
Patient Expiration (if single source)	August 29, 2006	January 23, 2005
Manufacturer (if single source)	Purdue Pharma	Janssen
Dosage forms / route of admin	Sustained Release Tablets- 10 mg, 20 mg, 40 mg, 80 mg	Transdermal patches - 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, 100 mcg/hr
Dosing frequency	generally BID	Generally Q3days
General dosing guidelines	▪ 80 mg should be used in opiod-tolerant patients only ▪ Tablets are to be taken whole, and are not to be broken, chewed, or crushed.	▪ Elderly, cachectic, or debilitated patients may have altered pharmacokinetics and should not be started on doses higher than 25 mcg/h unless they are already taking more than 135 mg of oral morphine a day (or an equivalent opiate dose) ▪ dosage should be individualized – including an evaluation of pre-existing opioid tolerance.
Pediatric Labeling	Safety and efficacy not established in patients below the age of 18	Safety and efficacy not established in patients below the age of 2
FDA Labeled Indications	▪ Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time ▪ OxyContin® is not intended for use as a prn analgesic.	Management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids. Should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result.

Characteristic	Oxycodone Hydrochloride Extended Release	Fentanyl Transdermal
	Oxycontin®	Duragesic®
Contraindications	▪ Hypersensitivity to oxycodone ▪ Known or suspected paralytic ileus ▪ Constipation ▪ Use with caution in patients with head injury and increased intracranial pressure ▪ Hypotension ▪ GI obstruction ▪ Acute or severe bronchial asthma	▪ patients with known hypersensitivity to fentanyl or adhesives. ▪ In the management of acute or post-operative pain, including use in out-patient surgeries because there is no opportunity for proper dose titration ▪ In the management of mild or intermittent pain that can otherwise be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids, and ▪ In doses exceeding 25 µg/h at the initiation of opioid therapy because of the need to individualize dosing by titrating to the desired analgesic effect.
Drug Interactions	▪ Potential for additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. ▪ Potential for interactions with drugs metabolized by P450 2D6	▪ CYP3A4 Inhibitors: May cause decreased clearance of fentanyl. ▪ CYP3A4 Inducers such as rifampin, carbamazepine, and phenytoin, may cause increased clearance of fentanyl.
Major AEs / Warnings	▪ respiratory depression, constipation, nausea, somnolence, dizziness, pruritis ▪ potential for abuse and addiction ▪ use with caution in head injury ▪ hypotension ▪ not indicated for use in the immediate post-operative period in OxyContin® naïve patients ▪ use with caution in patients with biliary tract disease ▪ Oxycodone may produce release of histamine ▪ increased potential risks and should be used only with caution in the following conditions: acute alcoholis m; adrenocortical insufficiency, CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.	▪ Fever, vomiting, nausea, constipation, drowsiness, sweating, bradycardia ▪ Potential for abuse and/or addiction ▪ Usually no major effects on the cardiovascular system at therapeutic doses, however, some patients may develop orthostatic hypotension ▪ Clinically significant histamine release only rarely occurs with fentanyl. Assays in man show no clinically significant histamine release in dosages up to 50 mcg/kg.

Characteristic	Oxycodone Hydrochloride Extended Release	Fentanyl Transdermal
	Oxycontin®	Duragesic®
Pharmacokinetics issues	▪ food – no significant effect ▪ females have plasma concentrations up to 25% higher than males (weight adjusted)	▪ Duragesic® releases fentanyl from the reservoir at a nearly constant rate
Geriatric	▪ Plasma concentrations increased in elderly by 15% ▪ Pregnancy Category B ▪ Use not recommended in nursing mothers ▪ Hepatic Impairment – initiate therapy at 1/3 to ½ usual doses ▪ Renal Impairment – Increased plasma levels (˜50% higher with Clcr < 60 ml/min)	▪ Fentanyl clearance may be decreased in patients over 60 years of age ▪ Pregnancy Category C ▪ Use not recommended in nursing mothers ▪ Use with caution in patients with hepatic and/or renal impairment
Notes:	▪ OxyContin® 10 mg every 12 hours produced an equivalent AUC and Cmax and similar Cmin compared to 5 mg of the immediate release tablets administered every 6 hours. There is less fluctuation in plasma concentrations with OxyContin. ▪ Onset of analgesic effect occurs within 1 hour in most patients following oral administration.	▪ At equivalent analgesic serum concentrations, fentanyl and morphine produce a similar degree of hypoventilation. ▪ After removal of the transdermal patch, serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 (range 13-22) hours. ▪ The transdermal patches must not be cut or damaged, this destroys the control delivery system. ▪ If exposed to external heat sources there is the potential for clinically significant increases in the release rate o fentanyl. This includes the use of heating pads, electric blankets, saunas, and hot tubs.

References

1. Electronic Orange Book: http://www.fda.gov/cder/ob/default.htm
2. Selevan J, Cada D eds. The Formulary Monograph Service. http://www.formularymonographs.com/default.asp
3. Pharmacy Benefits Management Strategic Healthcare Group, Department of Veterans Affairs. http://www.vapbm.org/PBM/menu.asp
4. Hutchison TA & Shahan DR (Eds): DRUGDEX® System. MICROMEDEX, Greenwood Village, Colorado (Edition expires 12/2003)
5. Avinza®. Prescribing information. Accessed at Drugs.com. Jan 2004.
6. Duragesic®. Prescribing information. Accessed at Drugs.com. Jan 2004.
7. Kadian®. Prescribing information. Accessed at Drugs.com. Jan 2004.
8. MSContin® Prescribing information. Accessed at Drugs.com. Jan 2004.
9. OxyContin®. Prescribing information. Accessed at Drugs.com. Jan 2004.

Characteristic	Methylphenidate		
	Ritalin® Ritalin SR® Ritalin LA® Methylin®, Methyl ER®	Metadate ER® Metadate CD®	Concerta®
Pharmacology	Methylphenidate is a CNS stimulant that is thought to exert its pharmacological activity be blocking the reuptake of norepinephrine and dopamine. Methylphenidate is a racemic mixture of the d- and l-threo enantiomers. The d-threo- enantiomer has greater pharmacologic activity.		
Date of FDA Approval	Ritalin® LA – June 5, 2002	Metadate® CD - April 3, 2001	August 1, 2001
Generic available?	Ritalin – yes Ritalin SR – yes Ritalin LA - no	Metadate ER – yes Metadate CD - no	No
Patent Expiration (if single source)	May 1, 2019	October 27, 2020	March 16, 2004
Manufacturer (if single source)	Novartis	Metadate® CD - Celltech	McNeil
Dosage forms / route of admin	Immediate release - 2.5, 5, and 10 mg Extended release – 10 mg and 20 mg Ritalin® LA – 20, 30, and 40 mg capsules	Metadate ®ER – 10, 20 and 30 mg Metadate CD capsules 10 mg (3mg IR; 7 mg ER), 20 mg (6 mg IR; 14 mg ER), or 30 mg (9 mg IR; 21 mg ER)	Extended release tablets – 18, 27, 36 and 54 mg
Dosing frequency	Immediate release – BID-TID Sustained release – BID Ritalin LA - QD	QD	QD
General dosing guidelines	▪ The recommended starting dose is 20 mg QD, maximum dose = 60 mg QD. ▪ Ritalin LA – capsule should be swallowed whole or the capsule may be opened and the contents sprinkled on a small amount of applesauce. The contents of the capsule should not be crushed or chewed.	▪ The recommended starting dose is 20 mg QD, maximum dose = 60 mg QD. ▪ Capsules should be swallowed whole or the capsule may be opened and the contents sprinkled on a small amount of applesauce. The contents of the capsule should not be crushed or chewed	▪ Recommended starting dose = 18 mg QD. Maximum dose = 54 mg QD. ▪ May be administered with or without food. ▪ Capsule must be swallowed whole.
Pediatric Labeling	Safety and efficacy not established in children under age 6.		

Characteristic	Methylphenidate		
	Ritalin® Ritalin SR® Ritalin LA® Methylin®, Methyl ER®	Metadate ER® Metadate CD®	Concerta®
FDA Labeled Indications	▪ treatment of ADHD ▪ narcolepsy (immediate release and Methylin ER)	▪ treatment of ADHD	▪ Treatment of ADHD
Other Studied Uses	▪ Fatigue, disease related ▪ Depression ▪ Autism		
Contraindications	▪ Hypersensitivity to methylphenidate ▪ Mot or tics or a diagnosis or family history of Tourette's syndrome ▪ Glaucoma ▪ Use during or within 14 days following the use of a MOA Inhibitor (hypertensive crisis may occur) ▪ Agitated states		
Drug interactions	▪ Methylphenidate may decrease the effectiveness of antihypertensive agents. ▪ Methylphenidate may inhibit the metabolism of warfarin, phenytoin, phenobarbital, primidone, SSRIs, and tricyclic antidepressants		
Major AEs / Warnings	▪ Nervousness, headache, insomnia, upper abdominal pain, decreased appetite, anorexia, tachycardia ▪ Decreases in predicted growth rate (weight gain/height) have been reported with long-term use of stimulants in children. ▪ May lower the seizure threshold		
			▪ One long-term study showed an 8% incidence of new onset tics. ▪ Tablet is nondeformable and does not significantly change in shape in the GI tract. Use is not recommended in patients with preexisting severe gastrointestinal narrowing. ▪ Not recommended for treatment of depression. ▪ Use not recommended for the prevention or treatment of normal fatigue states.

Characteristic	Methylphenidate		
	Ritalin® Ritalin SR® Ritalin LA® Methylin®, Methyl ER®	Metadate ER® Metadate CD®	Concerta®
Pharmacokinetic Issues	▪ Ritalin® LA – the absorption profile has two peaks approximately four hours apart	▪ Metadate® CD capsules contain immediate release (30% of the dose) and sustained release (70% of the dose) beads. This produces an initial peak similar to an immediate release tablet followed by another peak approximately 3 hours later.	▪ Concerta® tablets produce an initial peak in one to two hours, then increasing gradually to a Cmax at 6 to 8 hours.
Key Populations	▪ Pregnancy Category: C ▪ Renal and hepatic insufficiency should have minimal effects on the pharmacokinetics of methylphenidate ▪ For Concerta, AUC was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics		
Notes:	▪ Capsules of Ritalin® LA may be opened and administered with applesauce. ▪ Relative bioavailability of Ritalin® LA given QD is comparable to the same total daily dose of Ritalin given in two doses four hours apart. ▪ Ritalin®LA – the absorption profile has two peaks approximately four hours apart – each representing 50% of the dose	▪ Capsules of Metadate® CD may be opened and administered with applesauce. ▪ Metadate CD capsules contain immediate release (30% of the dose) and sustained release (70% of the dose) beads. This produces an initial peak similar to an immediate release tablet followed by another peak approximately 3 hours later.	▪ Concerta® tablets must be swallowed whole. ▪ Tablet has 22% of the dose in overcoat, the remaining dose is released through a controlled release process from a trilayer core ▪ The tablet shell and some insoluble core components is eliminated from the body. Patients may notice something that looks like a tablet in their stool. ▪ Once daily Concerta® has comparable bioavailability to methylphenidate TID, however Concerta QD minimizes the trough to peak fluctuations seen with methylphenidate TID.
	▪ At least 80% of children will respond to one of the stimulants. Children failing to respond or having intolerable side effects on one stimulant should be tried on another stimulant. ▪ Group studies of stimulants have failed to show any consistent, significant differences between treatments. ▪ There are large individual differences in patients' responses to different drugs and doses. Best order of presentation for a particular patient is not known.		

Characteristic	Dexmethylphenidate	Dextroamphetamine	Amphetamine/ Dextroamphetamine
	Focalin®	Dexedrine® DextroStat®	Adderall® Adderall XR®
Pharmacology	Methylphenidate hydrochloride is a CNS stimulant that blocks the reuptake of norepinephrine and dopamine. Dexmethylphenidate is the more pharmacologically active enantiomer.	Dextroamphetamine is a non-catecholamine, sympathomimetic amine with CNS stimulant activity. They also cause elevations in blood pressure and weak respiratory stimulation.	Adderall® combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate.
Date of FDA Approval	November 13, 2001	Before Jan 1982	XR – October 11, 2001
Generic available?	No	Yes	Adderall® XR - No
Patent Expiration (if single source)	December 4, 2015		October 21, 2018
Manufacturer (if single source)	Novartis		Shire
Dosage forms	Tablets – 2.5 mg, 5mg, 10 mg	Immediate release tablets – 5 and 10 mg Sustained release capsules – 5, 10 and 20 mg	Capsules – 5, 10, 15, 20, 25 and 30 mg
Dosing frequency	BID – at least 4 hours apart	Spanules – QD Tablets - BID	QD
General dosing guidelines	▪ starting dose = 2.5 mg BID ▪ maximum dose = 10 mg BID	▪ Starting dose for age 3 to 5 = 2.5 mg for age 6 and older = 5 mg QD-BID. ▪ Maximum dose = 40 mg ▪ For narcolepsy: Usual dose 5 mg to 60 mg per day	Immediate release ▪ Starting dose for age 3 to 5 = 2.5 mg for age 6 and older = 5 mg QD-BID. ▪ Maximum dose = 40 mg ▪ For narcolepsy: Usual dose 5 mg to 60 mg per day Extended release ▪ Starting dose for age 6 and older = 10 mg QAM ▪ Maximum dose = 30 mg/day

Characteristic	Dexmethylphenidate	Dextroamphetamine	Amphetamine/ Dextroamphetamine
	Focalin®	Dexedrine® DextroStat®	Adderall® Adderall XR®
Pediatric Labeling	Safety and efficacy have not been established in children under age 6.	Amphetamines are not recommended for use in patients under 3 years of age.	
			ADDERALL XR® is not indicated for use in children less than 6 years of age.
FDA Labeled Indications	▪ treatment of ADHD	▪ Narcolepsy ▪ ADHD	▪ Immediate release – treatment of ADHD and narcolepsy ▪ Sustained release - treatment of ADHD
Other Studied Uses		▪ Depression ▪ Obesity	▪ Depression
Contraindications	▪ Hypersensitivity to methylphenidate ▪ Motor tics or a diagnosis or family history of Tourette's syndrome	▪ History of drug abuse ▪ Advance arterioslerosis ▪ Symptomatic cardiovascular disease ▪ Moderate to severe hypertension ▪ Hypersensitivity to sympathomimetic amines	
	▪ Glaucoma ▪ Use during or within 14 days following the use of a MOA Inhibitor (hypertensive crisis may occur) ▪ Agitated states		
Drug Interactions	▪ Methylphenidate may decrease the effectiveness of antihypertensive agents. ▪ Methylphenidate may inhibit the metabolism of warfarin, phenytoin, phenobarbital, primidone, SSRIs, and tricyclic antidepressants	▪ Andrenergic blockers ▪ Tricyclic antidepressants – increased amphetamine effects ▪ MAO Inhibitors – significant increase in amphetamine effects ▪ Haldol/chlorpromazine ▪ Lithium ▪ Meperidine ▪ Phenytoin/Phenobarbital – may have delayed intestinal absorption ▪ Acidifying agents (ascorbic acid) – decreased absorption ▪ Antacids – increased absorption ▪ Urinary alkalinizing agents – decreased urinary excretion ▪ Urinary acidifying agents (ex. Ammonium chloride) – increased urinary excretion	

Characteristic	Dexmethylphenidate	Dextroamphetamine	Amphetamine/ Dextroamphetamine
	Focalin®	Dexedrine® DextroStat®	Adderall® Adderall XR®
Major AEs / Warnings	▪ Nervousness, headache, insomnia, upper abdominal pain, decreased appetite, anorexia, tachycardia ▪ Focalin is not recommended for the treatment of depression or for the treatment or prevention of normal fatigue states ▪ May exacerbate symptoms of psychosis ▪ May lower the seizure threshold ▪ Use with caution in patients with hypertension, recent MI, heart failure, hyperthyroidism ▪ The safety of long-term use of Focalin® in children and effects on growth have not been established. Decreases in predicted growth rate (weight gain/height) have been reported with long-term use of stimulants in children.	▪ Insomnia, loss of appetite, abdominal pain, nausea, vomiting, emotional lability ▪ Elevations in plasma corticosteroid levels ▪ Use with caution in patients with even mild hypertension ▪ Decreases in predicted growth rate (weight gain/height) have been reported with long-term use of stimulants in children. ▪ Use with caution in patients with motor tics, Tourette's syndrome or a family history of Tourette's syndrome ▪ May exacerbate symptoms of psychosis	
Pharmacokinetics issues	Can be administered without regard to food		Adderall XR® capsules contain two types of beads designed to produce a "double-pulsed" delivery formulation.
Key Populations	Category: C		
	▪ Per the manufacturer, there is insufficient experience with the use of Focalin to detect ethnic variations in pharmacokinetics. ▪ Renal and hepatic insufficiency should have minimal effects on the pharmacokinetics.	Amphetamine pharmacokinetics appear to be comparable in Caucasians, African-Americans and Hispanics.	

Characteristic	Dexmethylphenidate	Dextroamphetamine	Amphetamine/ Dextroamphetamine
	Focalin®	Dexedrine® DextroStat®	Adderall® Adderall XR®
Notes:	For patients currently taking methylphenidate, the recommended starting dose of Focalin® is one-half the current dose of racemic methylphenidate.		▪ Adderall XR ®20 mg QD produces similar plasma concentration profiles to the immediate release product administered as 10 mg BID (four hours between doses) ▪ Tmax for Adderall XR® is 7 hours (four hours longer than that observed with the immediate release product. ▪ When switching from Adderall® to Adderall XR® the same total daily dose can be administered as Adderall XR QD (in the morning to minimize potential for insomnia).
	▪ At least 80% of children will respond to one of the stimulants. Children failing to respond or having intolerable side effects on one stimulant should be tried on another stimulant. ▪ Group studies of stimulants have failed to show any consistent, significant differences between treatments. ▪ There are large individual differences in patients' responses to different drugs and doses. Best order of presentation for a particular patient is not known.		

Characteristic	Atomoxetine	Modafinil
	Strattera®	Provigil®
Pharmacology	Exact mechanism of action is not known. Efficacy in treating ADHD is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter.	Exact mechanism of action is not known. In addition to promoting wakefulness it also causes psychoactive and euphoric effects similar to other CNS stimulants. Structurally distinct from methylphenidate and amphetamine.
Date of FDA Approval	November 26, 2002	December 24, 998
Generic available?	No	No
Patent Expiration (if single source)	July 11, 2015	August, 2006
Manufacturer (if single source)	Lilly	Cephalon
Dosage forms / route of admin	Oral capsules - 10, 18, 25, 40, and 60 mg	Oral tablets – 100 mg and 200 mg
Dosing frequency	QD - BID	QD
General dosing guidelines	▪ Children and adolescents up to 70 kg Starting dose = 0.5 mg/kg/day Maximum dose = 1.4 mg/kg or 100 mg daily (whichever is less) ▪ Patients over 70 kg Starting dose = 40 mg/day Maximum dose = 100 mg daily	▪ Recommended dose = 200 mg qd ▪ Doses of 400 mg daily have been well tolerated, but may not offer specific patients any additional benefit.
Pediatric Labeling	Safety and efficacy not established in children under age six.	Safety and effectiveness not established in children less than 16.
FDA Labeled Indications	Treatment of ADHD	▪ To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy ▪ Very recent approvals for (approval wording still pending) ➢ Shift work sleep disorder ➢ Treatment of excessive daytime sleepiness with obstructive sleep apnea as an adjunct to CPAP

Characteristic	Atomoxetine	Modafinil
	Strattera®	Provigil®
Other Studied Uses	▪ Depression	▪ Fatigue associate with Multiple Sclerosis ▪ Fatigue associated with Parkinson's disease ▪ ADHD
Contraindications	▪ Hypersensitivity to atomoxetine ▪ Use during or within 14 days following the use of a MOA Inhibitor. A MOAI should not be initiated within 14 days of atomoxetine use. ▪ Narrow angle glaucoma	▪ Hypersensitivity to modafinil.
Drug Interactions	▪ Coadministration with albuterol may potentiate albuterol induced increases in blood pressure and heart rate ▪ Coadministratin of CYP2D6 inhibitors (paroxetine, fluoxetine, quinidine) may require dose adjustment of Strattera in normal metabolizers of this enzyme. Dosage adjustment should not be necessary in poor metabolizers.	▪ May cause induction of CYP3A4 – substrates of this enzyme (steroidal contraceptives, cyclosporine, theophylline) may require dosage adjustments ▪ May cause induction of its own metabolism (CYP3A4). Inducers of this enzyme (carbamazepine, phenobarbital, rifampin) or inducers (ketoconazole, itraconazole) may alter the levels of modafinil. ▪ Use with caution with MAO inhibitors ▪ The effectiveness of steroidal contraceptives may be reduced. Alternate methods of contraception are recommended during therapy with modafinil and for one month after discontinuation of therapy. ▪ Patients on concurrent phenytoin should be monitored for phenytoin toxicity ▪ Monitoring of INR is recommended for the first several months of concurrent therapy and if modafinil dose is changed
Major AEs / Warnings	▪ Increases in blood pressure and heart rate – use with caution in patients with hypertension, tachycardia, cardiovascular or cerebrovascular disease ▪ Dyspepsia, nausea, vomiting, fatigue, decreased appetite ▪ Rare hypersensitivity reactions – including rash, urticaria, angioneurtoic edema ▪ Growth should be monitored during treatment with Strattera®. There are no long-term, placebo-controlled studies evaluating the effect of Strattera on growth. Acute treatment studies showed some potential effects	▪ The most commonly observed adverse events (>/=5%) associated with the use of modafinil more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, anxiety, and insomnia. ▪ Use not recommended in patients with LVH, ischemic EKG changes, angina or arrhythmia.

Characteristic	Atomoxetine	Modafinil
	Strattera®	Provigil®
Pharmacokinetics issues	▪ Strattera® can be administered with or without food. ▪ Strattera® is metabolized by CYP2D6. A portion of the population ((about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These patients may have a 5 fold increase in Cmax, a 10 fold increase in AUC and slower elimination when compared to normal metabolizers.	▪ Food causes no change in AUC, but may delay Tmax by approximately one hour. ▪ After chronic use of dose = 400 mg/day, Provigil showed a possible induction of its own metabolism
Key Populations	• The safety and efficacy of Strattera® in geriatric patients have not been established • Pregnancy Category: C • No affect on atomoxetine pharmacokinetics (except that PM's are more common in Caucasians). ▪ No dosage adjustment necessary for renal insufficiency or ESRD. • Dosage adjustment is necessary with hepatic impairment. Patients with moderate hepatic impairment should receive 50% of the normally recommended dose, if severe hepatic impairment the dose should only be reduced to 25% of the normal dose.	• To the extent that elderly patients may have diminished renal and/or hepatic function, dosage reductions should be considered • Pregnancy Category: C • The effect of race on modafinil pharmacokinetics is not known. • Renal impairment did not result in increased modafinil exposure, but exposure to an inactive metabolite can be increased nine fold. • For patients with severe hepatic impairment the dose should be reduced by half.
Notes:	• Unlike stimulants, somnolence is a common side effect – occurring 6 of 10 adolescents • "Abnormal thinking " may be less common with atomoxetine when compared to stimulants. • Not a controlled substance (unlike stimulants)	• Nighttime sleep measured with nocturnal polysomnography was not affected by the use of Provigil®. • Schedule IV (all other stimulants reviewed are CII) • Use not associated with clinically significant weight changes • No consistent changes observed in vital signs
Cylert® (pemoline) is also available for use in the treatment of ADHD. Due to the availability of other agents and the risk of potential life threatening liver failure it is no longer recommended as a first line agent and was not reviewed. It is available generically.		

References

1. Electronic Orange Book: http://www.fda.gov/cder/ob/default.htm
2. Selevan J, Cada D eds. The Formulary Monograph Service. http://www.formularymonographs.com/default.asp
3. Pharmacy Benefits Management Strategic Healthcare Group, Department of Veterans Affairs. http://www.vapbm.org/PBM/menu.asp
4. Hutchison TA & Shahan DR (Eds): DRUGDEX® System. MICROMEDEX, Greenwood Village, Colorado (Edition expires 12/2003)
5. American Academy of Pediatrics. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108(4):1033-44.
6. Wolfraich M, Greenhill L, Pelham W, etal. Randomized, controlled trial of OROS methylpheidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108(4):883-92.
7. Taylor FB, Russo J. Efficacy of modafinil compared to destoamphetamine for the treatment of attention deficit/hyperactivity disorder in adults. L Child Adolesc Psychopharmacol. 2000;10(4):311-20.
8. Adderall® XR. Prescribing Information. Accessed at drugs.com Jan 2004.
9. Concerta®. Prescribing In formation. Accessed at drugs.com Jan 2004.
10. Dexedrine®. Prescribing Information. Accessed at drugs.com Jan 2004.
11. Focalin® Prescribing Information. Accessed at drugs.com Jan 2004.
12. Metadate® CD. Prescribing Information. Accessed at drugs.com Jan 2004.
13. Ritalin®. Prescribing Information. Accessed at drugs.com Jan 2004.
14. Ritalin® LA. Prescribing Information. Accessed at drugs.com Jan 2004.
15. Ritalin® SR. Prescribing Information. Accessed at drugs.com Jan 2004.
16. Provigil®. Prescribing Information. Accessed at drugs.com Jan 2004.
17. Strattera®. Prescribing Information. Accessed at drugs.com Jan 2004.

Characteristic	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin
	Erythromycin base, Erythromycin estolate, Erythromycin stearate, Erythromycin ethylsuccinate	Zithromax®	Biaxin®, Biaxin XL®	Dynabac®
Pharmacology	Erythromycin attaches to the 50S subunit of the bacterial ribosome. Although the exact stage of protein synthesis affected by erythromycin is unknown, it may interfere with the translocation reaction. The growing peptide chain with its t-RNA moves from the 'acceptor site' to the 'donor site' on the ribosome. Erythromycin most likely binds to the donor site, preventing the translocation of the peptide chain. An in-vitro study showed that erythromycin induces neutrophil apoptosis in a dose-dependent manner and directly proportional to duration of erythromycin exposure. In vivo, enhanced neutrophil apoptosis caused by erythromycin may inhibit tissue damage and inflammation by limiting the capacity of neutrophils to generate potentially injurious responses to inflammatory mediators. This mechanism may account for the efficacy of erythromycin in cases of diffuse panbronchiolitis and chronic sinusitis, even when the causative agent is Pseudomonas aeruginosa, a bacterium which is insensitive to erythromycin.	Azithromycin is the prototype of a subclass of macrolide antibiotics known as the azalides (Bright et al, 1988). This agent differs structurally from erythromycin by insertion of a methyl-substituted nitrogen at position 9a in the lactone ring, creating a 15-membered macrolide. The antibacterial action of azithromycin is similar to erythromycin. Azithromycin inhibits messenger RNA directed polypeptide and protein synthesis. It exerts this activity by binding at the 50 S ribosomal subunit Azithromycin has been found to have significant post-antibiotic effect in susceptible strains of microorganisms. The average length of post-antibiotic effect was 3.5 hours for S pyogenes and S pneumoniae, 3 hours for M catarrhalis and H influenzae, and 2 hours for Klebsiella species	Clarithromycin is a macrolide antibiotic which binds to the 50S subunit of the bacterial ribosome. By the binding to the ribosome, protein synthesis is inhibited. Chemically, clarithromycin differs from erythromycin only in that it possesses a methoxy group rather than a hydroxyl group at position 6 of the macrolide ring. This not only makes the compound more stable in the presence of gastric acid, but also changes its metabolic fate such that a very active 14-hydroxy-clarithromycin metabolite is formed; this metabolite is twice as active than the parent compound against Haemophilus influenzae but is 4 to 7 times less active against MAC isolates. Clarithromycin is active against a host of aerobic and anaerobic gram-positive and gram-negative bacteria, as well as most Mycobacterium avium complex (MAC) bacteria. The clinical role of the 14-hydroxyl clarithromycin metabolite against susceptible bacteria has not been evaluated	Dirithromycin is a semisynthetic 14-member macrolide metabolized to an active compound, erythromycylamine. It is structurally related to erythromycin and clarithromycin. The oxygen at the C_9 position of erythromycin-A was modified to inhibit the decomposition of the agent under acidic conditions. Dirithromycin has a spectrum of activity similar to erythromycin.

Characteristic	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin
	Erythromycin base, Erythromycin estolate, Erythromycin stearate, Erythromycin ethylsuccinate	Zithromax®	Biaxin®, Biaxin XL®	Dynabac®
Date of FDA Approval		Nov 1991	Oct 1991	Aug 1995
Generic available?	Yes	No	No	No
Patent Expiration (if single source)		There are no unexpired patents for this product in the Orange Book Database	There are no unexpired patents for this product in the Orange Book Database	There are no unexpired patents for this product in the Orange Book Database
Manufacturer (if single source)		Pfizer	Abbott	Bock Pharmacal/Lilly
Dosage forms / route of admin	▪ Tablets – EC and film coated ▪ Capsules ▪ IV (not in PDL)	Suspension: Single dose 1 gram packets of azithromycin should be reconstituted with 60 mL of water and the re-constituted mixture consumed immediately. Tablets	granules for oral suspension, immediate-release tablets (Biaxin® Filmtab), extended-release tablets (Biaxin® XL Filmtab).	enteric coated, 250 mg tablets
Dosing frequency	q 6h – q 12h	Once daily	BID (IR) Once daily (XL)	Once daily
General dosing guidelines	The usual recommended dose is erythromycin 250 mg every 6 hours. If twice daily dosing is desired, the recommended dose is 500 mg every 12 hours. Higher doses may be used depending on the severity of infection with the maximum daily dose at 4 grams. Twice daily dosing is not recommended if using doses larger than 1 g Capsules containing enteric-coated pellets of erythromycin (ERYC®) may be opened and sprinkled on apple sauce for	The usual adult dose is 500 mg on the first day as a single dose followed by 250 mg once daily. A single 1 gram oral dose has been effective in sexually transmitted infections. For the prevention of Mycobacterium avium complex (MAC) infection, the recommended dosage of azithromycin is 1200 mg once weekly. For the treatment of disseminated	Typical oral adult doses for immediate-release clarithromycin are 250 to 500 mg twice a day. For the extended-release formulation, the recommended adult oral dose is 1000 mg (2 x 500 mg) once daily. In children, the recommended dose is 15 mg/kilogram/day in 2 divided doses. For Helicobacter infections, the recommended dosage for	Dirithromycin 500 mg once daily should be administered for 7 days in the treatment of bronchitis and skin and skin structure infections, for 10 days in the treatment of pharyngitis/tonsillitis and for 14 days in the treatment of community-acquired pneumonia. It should be taken with food or within 1 hour eating.

Characteristic	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin
	Erythromycin base, Erythromycin estolate, Erythromycin stearate, Erythromycin ethylsuccinate	Zithromax®	Biaxin®, Biaxin XL®	Dynabac®
	administration to patients that are unable to swallow the capsule whole.	MAC infection, the recommended dose is 600 mg daily in combination with ethambutol 15 mg/kilogram (kg)/day. For pediatric patients, the dosage ranges from 5 mg/kg to 30 mg/kg once daily depending on the indication.	immediate-release clarithromycin is 500 mg 2 to 3 times daily in combination with other anti-H pylori drugs; low-dose regimens which used clarithromycin 250 mg have also been effective. clarithromycin oral suspension and immediate release tablets can be taken with or without food	
Pediatric Labeling	Yes	Yes	The use of clarithromycin immediate-release and granules have been evaluated in children. However, the extended-release clarithromycin formulation (Biaxin® XL) has not been evaluated in children	Safety and efficacy have not been established for children less than 12 years of age.[1]

Characteristic	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin
	Erythromycin base, Erythromycin estolate, Erythromycin stearate, Erythromycin ethylsuccinate	Zithromax®	Biaxin®, Biaxin XL®	Dynabac®
FDA Labeled Indications	Acne vulgaris Amebiasis Amebic colitis Bacterial endocarditis - prophylaxis Chlamydia infections Chlamydia trachomatis Chlamydial infections in pregnancy Conjunctivitis Endocervical infections Entamoeba histolytica Haemophilus influenzae infections Legionella micdadei pneumonia Legionella pneumophila Legionnaires' disease Listeriosis Mycoplasma pneumonia Neonatal conjunctivitis Neonatal pneumonia Nongonococcal urethritis Ophthalmia neonatorum Otitis media Pertussis Rectal infections Respiratory infections Rheumatic fever prophylaxis Skin and soft tissue infection Syphilis Treponema pallidum Uncomplicated urethral infections Urethritis Urogenital infections	Chancroid Chlamydia trachomatis infection Chronic obstructive pulmonary disease Community-acquired pneumonia Conjunctivitis COPD Gonorrhea Haemophilus infections Lower respiratory tract infections Moraxella infections Mycobacterium avium complex - prophylaxis Mycobacterium infections - treatment Otitis media Pelvic inflammatory disease Pharyngitis/tonsillitis PID Pneumonia Skin and skin structure infections Streptococcal infections Urethritis - cervicitis	Bronchitis Chronic bronchitis Helicobacter pylori - dual therapy Hemophilus infections Lower respiratory tract infection MAC Maxillary sinusitis Moraxella infections Mycobacterium avium complex - prophylaxis Mycobacterium avium complex - treatment Mycoplasma pneumoniae infections Otitis media Pharyngitis/tonsillitis Pneumonia Sinusitis acute maxillary Skin and skin structure infections Streptococcal infections TWAR	Acute bronchitis Bacterial pneumonia Bronchitis Chronic bronchitis Community-acquired pneumonia Pharyngitis Pneumonia - community acquired Skin and skin structure infections Tonsillitis

Characteristic	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin
	Erythromycin base, Erythromycin estolate, Erythromycin stearate, Erythromycin ethylsuccinate	Zithromax®	Biaxin®, Biaxin XL®	Dynabac®
Other Studied Uses	Bacillus calmette guerin (BCG) infections Bite injuries Blepharokeratitis Bronchitis Campylobacter jejuni infections Chancroid Corynebacterium jeikeium infections Diphtheria Gastroparesis Impetigo Lyme disease Preoperative bowel preparation Ureaplasm urealtyticum infections	Acne Cholera Cystic fibrosis Endocarditis prophylaxis Gingival hyperplasia - drug-induced Helicobacter pylori - triple therapy Legionella infections Lyme disease Mycoplasma pneumoniae infections Sinusitis	Anthrax Asthma Lyme disease Cyclosporine dose reduction Helicobacter pylori - triple-drug therapy Pertussis Pneumonia-legionella pneumophila	COPD
Contraindications	Hypersensitivity to macrolide antibiotic			
	Concomitant therapy with astemizole, terfenadine, cisapride, or pimozide		Concomitant therapy with cisapride, pimozide, astemizole, or terfenadine; increased risk of cardiac arrhythmias	
Drug interactions	▪ As a class, the macrolides have been studied and reviewed extensively in regards to their drug interaction profiles. In general, the macrolides are classified into three groups based on their inhibition of cytochrome P450 3A4 in vitro: ▪ Group 1 agents bind and strongly inhibit CYP 3A4. The group includes erythromycin. ▪ Group 2 agents have lower affinity for CYP 3A4 and form complexes to a lesser extents. The group includes clarithromycin ▪ Group 3 agents bind poorly to CYP 3A4 and have little inhibitory activity. The group includes azithromycin and dirithromycin. ▪ Dirithromycin does not significantly affect the pharmacokinetics of theophylline, terfenadine, cyclosporine or oral contraceptives. ▪ Drug interactions with macrolides may also occur via alterations in gastric emptying or by alteration of normal gastrointestinal microflora.[1] ▪ See Drug Interaction chart which follows table for specific drugs.			

Characteristic	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin
	Erythromycin base, Erythromycin estolate, Erythromycin stearate, Erythromycin ethylsuccinate	Zithromax®	Biaxin®, Biaxin XL®	Dynabac®
Major AEs / Warnings	Hepatic dysfunction Prevention of congenital syphilis; adequate drug concentrations may not be available to fetus; treat infants born to mothers treated with erythromycin during pregnancy with an appropriate penicillin Patients with myasthenia gravis; may exacerbate weakness Risk factors for arrhythmias (e.g., torsade de pointes) include: electrolyte abnormalities; concomitant use of Class Ia and Class III anti-arrhythmic drugs; rapid infusion ; elderly individuals Consideration for many significant drug-drug interactions Risk for infantile hypertrophic pyloric stenosis in infants receiving erythromycin therapy Elderly patients receiving intravenous erythromycin 4 grams/day or more; increase risk for drug-induced hearing loss, especially those with renal or hepatic impairment	Avoid oral therapy in pneumonia patients with the following risk factors: cystic fibrosis, nosocomial infections, bacteremia, hospitalization, elderly, or debilitated Individuals with prolonged QT interval Impaired liver function Creatinine clearance less than 10 mL/min No data are available for the prevention of rheumatic fever	▪ The most common adverse side effects in adults and pediatrics involve the gastrointestinal (GI) tract (e.g., diarrhea, nausea, vomiting, or abdominal pain); only 1% of patients experience severe GI side effects. ▪ Avoid clarithromycin in patients allergic to macrolide antibiotics. ▪ Use with caution in patients with marked renal or hepatic impairment.	▪ Adverse effects of dirithromycin are very similar to those seen with erythromycin. ▪ The most common are gastrointestinal and include abdominal pain, diarrhea, nausea, dyspepsia and flatulence. ▪ Other reported adverse effects include headache, somnolence, urticaria and vaginal moniliasis.[4,31]

Characteristic	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin
	Erythromycin base, Erythromycin estolate, Erythromycin stearate, Erythromycin ethylsuccinate	Zithromax®	Biaxin®, Biaxin XL®	Dynabac®
Pharmacokinetics issues	Absorption is variable but much better with the various salt forms compared to the base; the drug is widely distributed in body tissues; metabolism occurs in the liver by demethylation with excretion of 2.5% to 15% unchanged drug in the urine; additional excretion and sequestration occurs in bile. Erythromycin estolate (Ilosone®) suspension may be kept at room temperature for 14 days without significant loss of potency. The manufacturer recommends refrigeration to maintain optimal taste Erythromycin ethylsuccinate (EES® 200 and 400) liquids require refrigeration to preserve taste until dispensed. Refrigeration by the patient is not required if used within 14 days.	▪ Peak serum levels of azithromycin are observed 3 to 4 hours following oral administration; ▪ the oral bioavailability is reportedly 37%; ▪ tissue concentrations are significantly higher than serum levels; only small amounts of the drug are excreted in the urine, and the elimination half-life is biphasic. ▪ Oral suspension and tablets may be taken with or without food	▪ Clarithromycin is well absorbed from the gastrointestinal tract, with peak plasma concentrations occurring about 2 to 4 hours after oral administration; ▪ extensive tissue penetration is evident with the exception of the central nervous system. . ▪ Clarithromycin is metabolized to its active 14-hydroxy metabolite, and also N-demethylated; metabolites are primarily eliminated renally. ▪ Food will delay the absorption of immediate-release clarithromycin tablets however; the extent of absorption is not affected by food. May administer with or without food. ▪ Administering extended-release clarithromycin (Biaxin® XL) under fasting conditions is associated with a 30% lower clarithromycin AUC relative to administration with food. Should be administered with food	▪ Dirithromycin is characterized by low serum concentrations and high tissue levels. ▪ The drug is converted to an active metabolite (erythromycylamine) during absorption and distribution, which is the predominant compound found in plasma and extravascular tissues; ▪ Dirithromycin and erythromycylamine undergo minimal hepatic metabolism, and most of a dose of dirithromycin is excreted via the bile. ▪ Only small amounts appear unchanged in the urine (less than 3%); the elimination half-life of erythromycylamine ranges from 20 to 50 hours

Characteristic	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin
	Erythromycin base, Erythromycin estolate, Erythromycin stearate, Erythromycin ethylsuccinate	Zithromax®	Biaxin®, Biaxin XL®	Dynabac®
Special Populations	▪ Elderly patients receiving intravenous erythromycin at doses of 4 grams/day or more may be at an increased risk for developing drug-induced hearing loss, especially those with renal or hepatic impairment Pregnancy Category B Animal reproductive studies with erythromycin have demonstrated no evidence of teratogenicity. However, there are no well-controlled studies in pregnant women. Animal teratogenicity studies are not always predictive of human response. In view of these facts, erythromycin should only be considered during pregnancy if the potential benefit of the drug outweighs the potential risk to the fetus Erythromycin is excreted in human milk; caution should be used when this drug is administered to a nursing woman ▪ Patients with severe renal failure (GFR less than 10 mL/min) should receive 50 to 75% of the normal dose at the usual dosing interval. ▪ The maximum daily dose should not exceed 2 grams ▪ No dosage adjustment is necessary for patients with mild to moderate renal failure (GFR greater than 10 milliliters/minute)	Pregnancy Category B Animal studies using doses that exceed the recommended human dose of azithromycin have demonstrated no evidence of carcinogenicity or teratogenicity. However, there are no well-controlled studies in pregnant women. Animal teratogenicity studies are not always predictive of human response. General consideration should be given to this fact before administering azithromycin to women of childbearing potential, especially during the first trimester when maximum organogenesis takes place. ▪ No dosage adjustment is needed in patients with renal insufficiency; however, azithromycin should be used with caution in patients with a ClCr <10 mL/min	▪ Clarithromycin dosage adjustments are not required in healthy elderly patients. However, dosage adjustments should be considered in elderly patients with severe renal impairment Pregnancy Category C In animal studies, clarithromycin has had adverse effects on the outcome of pregnancy and/or the embryo-fetal development at doses producing serum levels 2 to 17 times therapeutic levels obtained in humans. Clarithromycin should not be used during pregnancy unless no alternative therapy is available ▪ In the presence of severe renal impairment (ie, ClCr <30 mL/min), the dose should be halved or the dosing interval doubled	▪ No dosage adjustments are necessary in elderly patients Pregnancy Category C There are no well-controlled studies in pregnant women. Dirithromycin should only be considered during pregnancy if the potential benefit of the drug outweighs the potential risk to the fetus ▪ Dosage reduction does not appear necessary in patients with renal impairment, including patients requiring dialysis

Characteristic	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin
	Erythromycin base, Erythromycin estolate, Erythromycin stearate, Erythromycin ethylsuccinate	Zithromax®	Biaxin®, Biaxin XL®	Dynabac®
Notes	▪ Erythromycin is an effective antimicrobial for infections caused by most of the gram-positive bacteria, with limited usefulness in staphylococcal and gram-negative infections. Resistance to erythromycin is commonly reported with hospital-acquired Staph, therefore, sensitivity testing is recommended prior to initiation of erythromycin therapy in this setting. ▪ Erythromycin is an appropriate alternative to penicillin and cephalosporin antimicrobials for infections with susceptible gram-positive and gram-negative bacteria. The drug is highly effective against Legionnaire's bacterium, Mycoplasma pneumonia, and Chlamydia trachomatis, and is the drug of first choice for these infections. ▪ Erythromycin has been successfully utilized for acne vulgaris, otitis media, Campylobacter enteritis, neonatal conjunctivitis, Legionnaire's disease, preoperative bowel preparation, mycoplasma infections, chlamydia infections and most infections caused by gram-positive organisms. ▪ The increased use of macrolide antibiotics has been correlated with increased resistance rates to erythromycin in isolates of *Group A Strepticocci*. Routine use of macrolides for the treatment of pharyngitis caused by group A streptococci is not recommended as susceptibilities of group A streptococci to antibiotics such as penicillin remain stable. ▪ The unfavorable pharmacokinetic profile (incomplete and unreliable absorption) of oral erythromycin frequently prevents it from being the drug of first choice, in favor of the new macrolides; clarithromycin and roxithromycin. ▪ Oral erythromycin is suggested by the American Heart Association as an alternative to clindamycin for prophylaxis of endocarditis for patients at risk undergoing dental, oral, or upper respiratory procedures, but allergic to amoxicillin or penicillin			
Pipeline Agents	▪ Roxithromycin is not being pursued in the United States. However, the drug is marketed in Italy, France, Germany, Switzerland, Netherlands, and South Africa. ▪ Telithromycin (Ketek®) is a semisynthetic derivative of erythromycin A belonging to the ketolides, a class of antibacterial agents related to macrolides. It is currently marketed in Europe, approved there in July 2001.			

Interacting Drugs	Erythromycin	Clarithromycin	Azithromycin
Theophylline	X	X	*
Digoxin	X	X	*
Oral anticoagulants	X	X	*
Ergotamine/ dihydroergotamine	X	X	*
Triazolam/ midazolam	X	X	*
Clozapine	X	X	
Carbamazepine	X	X	*
Cyclosporine	X	X	*
Felodipine	X	X	
Tacrolimus	X	X	
Methylprednisone	X	X	
Hexobarbital	X	X	*
Phenytoin	X	X	*
Alfentanil/sufentanil	X	X	
Cisapride	X	X	
Disopyramide	X	X	
HMG CoA reductase inhibitors	X	X	
Bromocriptine	X	X	
Valproate	X	X	
Terfenadine	X	X	*
Astemizole	X	X	
Pimozide	X	X	
Rifabutin	X	X	
Omeprazole		X	
Zidovudine		X	
Fluconazole		X	
Ritonavir		X	

*Although azithromycin has not been found to interact with these agents, the package insert specifies that caution should be used due to interactions found with other macrolides

References

1. Inamura K, Ohta N, Fukase S et al: The effects of erythromycin on human peripheral neutrophil apoptosis. Rhinology 2000; 38:124-129.
2. Electronic Orange Book: http://www.fda.gov/cder/ob/default.htm
3. Selevan J, Cada D eds. The Formulary Monograph Service. http://www.formularymonographs.com/default.asp
4. Pharmacy Benefits Management Strategic Healthcare Group, Department of Veterans Affairs. http://www.vapbm.org/PBM/menu.asp
5. Hutchison TA & Shahan DR (Eds): DRUGDEX® System. MICROMEDEX, Greenwood Village, Colorado (Edition expires 12/2003)

Characteristic	Second-Generation Quinolones		
	ciprofloxacin	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Noroxin®	Floxin®
Pharmacology	Quinolones affect bacterial cells by interfering with DNA and the enzyme DNA gyrase (topoisomerase II). The formation of the quinolone-gyrase-DNA complex prevents the DNA polymerase from proceeding at the replication fork, thus stopping DNA synthesis		
Date of FDA Approval	Oct 1987	Oct 1986	Dec 1990
Generic available?	No	No	No
Patent Expiration (if single source)	Feb 2011	Jan 2005	Sep 2003
Manufacturer (if single source)	Bayer	Merck	Ortho-McNeil
Dosage forms / route of admin	▪ Oral IR, oral ER, oral susp ▪ IV (not PDL) ▪ IR Tablet: 100, 250, 500, 750 mg ▪ ER Tablet: 500 mg ▪ Suspension: 250 or 500 mg/5mL	Tablet 400 mg	• Ophthalmic & Otic solutions (not PDL) • IV (not PDL) • Tablet: 200, 300, 400 mg
Dosing frequency	▪ IR: q 12 h ▪ ER: q 24 h	Q 12 hr	Q 12 hr

Characteristic	Second-Generation Quinolones		
	ciprofloxacin	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Noroxin®	Floxin®
General dosing guidelines	▪ IR: usually 500 mg q 12h (250-750 q 12h) ▪ ER: 500 mg q 24h (only indicated for acute uncomplicated UTI)	400 mg q 12 hr	▪ Chronic bronchitis: 400 mg IV or ORALLY every 12 hr for 10 days ▪ Community-acquired pneumonia: 400 mg IV or ORALLY every 12 hr for 10 days ▪ Cystitis: (E. coli, K. pneumoniae) 200 mg IV or ORALLY every 12 hr for 3 days ▪ Cystitis: (other approved organisms) 200 mg IV or ORALLY every 12 hr for 7 days ▪ Gonorrhea: 400 mg IV or ORALLY as a single dose ▪ Nongonococcal cervicitis/urethritis: 300 mg IV or ORALLY every 12 hr for 7 days ▪ Pelvic inflammatory disease: 400 mg IV or ORALLY every 12 hr for 10-14 days ▪ Prostatitis: 300 mg IV or ORALLY every 12 hr for 6 weeks ▪ Skin/skin structure infection: 400 mg IV or ORALLY every 12 hr for 10 days ▪ Urinary tract infection, complicated: 200 mg IV or ORALLY every 12 hr for 10 days

Characteristic	Second-Generation Quinolones		
	ciprofloxacin	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Noroxin®	Floxin®
Pediatric Labeling	▪ Safety and efficacy has not been established in children under 18 years old ▪ Although the safety and efficacy of ciprofloxacin has not been established in children under the age of 18, the morbidity and mortality associated with ANTHRAX drives a risk-benefit assessment that indicates the appropriateness of using ciprofloxacin for inhalational and cutaneous anthrax, as well as for postexposure prophylaxis in the pediatric population ▪ Clinical reviews and studies of children and infants have shown that intravenous or oral ciprofloxacin does not cause defects in linear growth, osteoarticular problems, or joint deformities	Safety and efficacy has not been established in children under 18 years old	▪ Safety and efficacy has not been established in children under 18 years old

Characteristic	Second-Generation Quinolones		
	ciprofloxacin	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Noroxin®	Floxin®
FDA Labeled Indications	▪ Anthrax - Postexposure Prophylaxis ▪ Bone And Joint Infection ▪ Bronchitis ▪ Conjunctivitis - Bacterial ▪ Corneal Ulcers ▪ Enterobacter Infections ▪ Febrile Neutropenia ▪ Gonorrhea ▪ Infectious Diarrhea ▪ Intra-Abdominal Infections ▪ Lower Respiratory Tract Infections ▪ Otitis Externa ▪ Prostatitis ▪ Proteus Indole - Positive Infections ▪ Proteus Mirabilis Infections ▪ Pseudomonal Infections ▪ Serratia Infections ▪ Shigella Infections ▪ Sinusitis ▪ Skin And Skin Structure Infections ▪ Staphylococcus Aureus Infections ▪ Streptococcus Pneumoniae ▪ Typhoid Fever ▪ Urinary Tract Infections	Urinary Tract Infections : ▪ Enterobacter UTI ▪ Escherichia Coli UTI ▪ Gonorrhea (urethritis) ▪ Klebsiella Pneumoniae UTI ▪ Prostatitis ▪ Proteus Indole-Positive UTI ▪ Proteus Mirabilis UTI ▪ Pseudomonal UTI ▪ Serratia UTI ▪ Staphylococcal UTI	• Susceptible infections due to S. pneumoniae, S. aureus, S. pyogenes, H. influenzae, P. mirabilis, N gonorrhoeae, C. trachomatis, E. coli, K. pneumoniae, P. aeruginosa • Chronic bronchitis, acute exacerbation • Community-acquired pneumonia • Conjunctivitis/corneal ulcers (ophthalmic solution) • Cystitis, uncomplicated • Gonorrhea • Nongonococcal urethritis and cervicitis (chlamydia) • Otitis media, acute with tympanostomy tubes (otic solution) • Otitis media, chronic suppurative with perforated tympanic membranes (otic solution) • Otitis externa (otic solution) • Pelvic inflammatory disease • Prostatitis • Skin/skin structure infection, uncomplicated • Urinary tract infections, complicated
Other Studied Uses	▪ Multi-drug resistance TB, ▪ cutaneous & GI anthrax, ▪ plague, ▪ tularemia, ▪ asymptomatic N. meningitis, ▪ chancroid, ▪ disseminated gonorrhea, ▪ granuloma inguinale, ▪ uncomplicated gonococcal infection of pharynx		▪ Acute salpingitis ▪ Bacterial infection and surgical prophylaxis ▪ Biliary tract infection ▪ Bone and joint infection ▪ Cholera ▪ Epididymitis ▪ Infectious diarrhea ▪ Leprosy ▪ Q fever ▪ Sepsis ▪ Shigella infection

Characteristic	Second-Generation Quinolones		
	ciprofloxacin	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Noroxin®	Floxin®
			▪ Typhoid fever
Contraindications	Hypersensitivity to any fluoroquinolones	▪ Hypersensitivity to norfloxacin or other fluoroquinolones ▪ History of tendonitis or tendon rupture on fluoroquinolone therapy	Hypersensitivity to any fluoroquinolones
Drug interactions	▪ Decreased GI absorption: sucralfate, iron salts, didanosine, antacids ▪ Theophylline ▪ Cimetidine ▪ Anticoagulants ▪ NSAIDs ▪ Antidiabetic agents		
	▪ Caffeine ▪ Cyclosporine ▪ Azlocillin	▪ Caffeine ▪ Cyclosporine ▪ Nitrofurantoin ▪ Probenecid	▪ Procainamide
Major AEs / Warnings	▪ GI, CNS most common adverse events; mild, may resolve with continued treatment ▪ Neurotoxicity; risk factors include renal failure, underlying CNS disease, and increased CNS penetration of the drug ▪ Tendinitis/tendon rupture: risk factors include patients over 60 years of age, renal failure, dialysis, concomitant corticosteroid therapy, and dyslipidemia ▪ Arthopathy ▪ Pts. with seizure hx ▪ QTc prolongation ▪ Phototoxicity ▪ Patients with myasthenia gravis; may exacerbate symptoms ▪ Patients with glucose 6-phosphate dehydrogenase deficiency		
Pharmacokinetics issues	Peak serum levels occur in 1 to 1.2 hours following PO doses; ciprofloxacin is metabolized in the liver to active metabolites, and 30% to 57% of a PO dose is recovered unchanged in the urine; the elimination half-life is 3 to 6 hours	Following a 400 mg dose in healthy volunteers, norfloxacin urinary concentrations remain above 30 mcg/mL for at least 12 hours. Since the MIC of norfloxacin for most bacteria is less than 4 mcg/mL, urinary concentrations of the drug given BID are more than adequate to provide bactericidal activity.	Ofloxacin is well absorbed after oral administration; administration with food causes only minor alterations in absorption. Ofloxacin is 20% to 32% plasma protein bound; the volume of distribution is 2.4 to 3.5 L/kg. Ofloxacin is excreted primarily unchanged in the urine with an elimination half-life of 5 to 7.5 hours.

Characteristic	Second-Generation Quinolones		
	ciprofloxacin	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Noroxin®	Floxin®
Key Populations	▪ Animal studies have not demonstrated that ciprofloxacin is teratogenic. However, there are no well-controlled studies in pregnant women. In view of these facts, ciprofloxacin should only be considered during pregnancy if the potential benefit of the drug outweighs the potential risk to the fetus. ▪ According the CDC, ciprofloxacin is the antibiotic of choice for initial prophylactic therapy for asymptomatic pregnant women exposed to B. anthracis. If the isolate is found to be penicillin-susceptable, amoxicillin may be considered to finish the 60-day prophylaxis course ▪ The manufacturer recommends no alterations in dose for patients age 65 years and older with normal renal function. In a retrospective analysis of 23 multiple-dose controlled trials, no overall differences in safety or effectiveness were observed between patients 65 and older, and younger patients. • Dose adjustments should be made for patients with a ClCr =50 mL/min: ➢ 30-50 mL/min: 250-500 mg q12h ➢ 5-29 ml/min: 250-500 mg q18h	▪ There has been no evidence of teratogenicity in animal species tested (rat, rabbit, mouse, monkey) at 6 to 50 times the usual human dose. ▪ There are no well-controlled teratogenic studies evaluating the effect of norfloxacin in pregnant women. ▪ In view of these facts, norfloxacin should only be considered during pregnancy if the potential benefit of the drug outweighs the potential risk to the fetus ▪ Dosing adjustments are not required in elderly patients who have a ClCr >25-30 mL/min. ▪ Norfloxacin may be used to treat urinary tract infections in elderly patients with a ClCr of 30 milliliters/minute/1.73 m^2 or less. The recommended dose is 400 mg once daily for the same duration as patients with normal renal function.	▪ Animal studies using doses that exceed the recommended human dose have shown that ofloxacin is fetotoxic. However, there are no well-controlled studies in pregnant women. ▪ In addition, ofloxacin is excreted into breast milk at concentrations similar to that observed in the plasma. ▪ In view of these facts, ofloxacin should only be considered during or after pregnancy if the potential benefit of the drug outweighs the potential risk to the fetus or nursing infant ▪ No specific geriatric recommendation but dose adjustments should be made for patients with a ClCr =50 mL/min: • 20-50 mL/min: usual dose q24h • <20 ml/min: ½ usual dose q24h

Characteristic	Second-Generation Quinolones		
	ciprofloxacin	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Noroxin®	Floxin®
Notes	• All of the fluoroquinolones are effective in treating urinary tract infections caused by susceptible organisms. • Ciprofloxacin remains effective in treating both urinary tract and systemic infections caused by P. aeruginosa, however the use of this agent continues to be limited by the increasing rates of resistance. • Ciprofloxacin: Only fluoroquinolone available as a suspension. Previously, ciprofloxacin was the most active fluoroquinolone against P. aeruginosa. Recent in vitro evidence suggests levofloxacin and gatifloxacin are as active against P. aeruginosa as ciprofloxacin.		

Third Generation Quinolones			
Characteristic	**gatifloxacin**	**gemifloxacin**	**levofloxacin**
	Tequin®	Factive®	Levaquin®
Pharmacology	Quinolones affect bacterial cells by interfering with DNA and the enzyme DNA gyrase (topoisomerase II). The formation of the quinolone-gyrase-DNA complex prevents the DNA polymerase from proceeding at the replication fork, thus stopping DNA synthesis		
	▪ Gatifloxacin is a fluoroquinolone with expanded activity against gram-positive organisms. In general, the in vitro activity of gatifloxacin is similar to or greater than that of other fluoroquinolones in clinical use against gram-positive and fastidious species ▪ Against anaerobes, gatifloxacin is more active than ciprofloxacin and ofloxacin, as active as tosufloxacin and sparfloxacin, and less active than trovafloxacin	▪ Gemifloxacin is a fluoroquinolone antimicrobial with a unique chemical structure. It is a fluoronaphthyridone carboxylic acid with a pyrrolidine substituent; these changes confer enhanced activity against gram-positive pathogens without significantly compromising gram-negative activity	▪ Ofloxacin exists as 2 optically-active isomers. Levofloxacin is the S(-)-enantiomer of ofloxacin, and is considered primarily responsible for the clinical antibacterial efficacy of the racemate. It is reportedly 8 to 128 times more potent than R(+)-ofloxacin and twice as potent as racemic ofloxacin. ▪ Results of some animal studies suggest that levofloxacin may have a lower propensity for adverse central nervous system effects than ofloxacin.
Date of FDA Approval	Dec 1999	Apr 2003	Dec 1996
Generic available?	No	No	No
Patent Expiration (if single source)	Dec 2015	Sept 2019	Dec 2010
Manufacturer (if single source)	Bristol-Myers Squibb	Genesoft	Ortho McNeil
Dosage forms / route of admin	▪ Tablet: 200 mg , 400 mg ▪ IV (not PDL)	▪ Tablet - 320 mg	▪ Tablet 250 mg, 500 mg, 750 mg ▪ IV & ophthalmic solution (not PDL)
Dosing frequency	once daily		

Third Generation Quinolones			
Characteristic	**gatifloxacin**	**gemifloxacin**	**levofloxacin**
	Tequin®	Factive®	Levaquin®
General dosing guidelines	▪ 400 mg daily	▪ chronic bronchitis: 320 mg daily for 5 days; ▪ community-acquired pneumonia: 320 mg daily for 7 days.	▪ Most indications: 500 mg every 24 hours for 7 to 14 days, depending on the indication. ▪ Complicated skin and skin structure infections and nosocomial pneumonia: 750 mg every 24 hours. ▪ UTI: 250 mg every 24 hours with a duration of 3 days for uncomplicated and 10 days for complicated infections
Pediatric Labeling	Safety and efficacy of oral or parenteral gatifloxacin have not been established in patients less than 18-years-old		
FDA Labeled Indications	▪ Bronchitis ▪ Cystitis ▪ Gonorrhea ▪ Pneumonia ▪ Pyelonephritis ▪ Sinusitis ▪ Skin & skin structure, uncomplicated ▪ Urinary tract infection	▪ Chronic bronchitis ▪ Community-acquired pneumonia	▪ Chronic bronchitis ▪ Chronic prostatitis ▪ Community-acquired pneumonia ▪ Conjunctivitis ▪ Nosocomial pneumonia ▪ sinusitis ▪ Skin and skin structure infection ▪ Urinary tract infections
Other Studied Uses	▪ Chlamydial infections ▪ Tuberculosis ▪ Chronic prostatitis		▪ Enteritis ▪ Gynecological infections ▪ Infectious diarrhea ▪ Otitis ▪ Chlamydia, ▪ Cervical, urethral, and rectal gonorrhea ▪ Pelvic inflammatory disease ▪ Tuberculosis (preferred oral agent for drug-resistant TB)
Contraindications	Hypersensitivity to any fluoroquinolones		

Third Generation Quinolones			
Characteristic	**gatifloxacin**	**gemifloxacin**	**levofloxacin**
	Tequin®	Factive®	Levaquin®
Drug interactions	▪ Decreased GI absorption: sucralfate, iron salts, didanosine, antacids ▪ Theophylline ▪ Cimetidine ▪ Anticoagulants ▪ NSAIDs ▪ antiarrhythmic agents		
	▪ probenecid		
Major AEs / Warnings	▪ GI, CNS most common adverse events; mild, may resolve with continued treatment ▪ Neurotoxicity; risk factors include renal failure, underlying CNS disease, and increased CNS penetration of the drug ▪ Tendinitis/tendon rupture: risk factors include patients over 60 years of age, renal failure, dialysis, concomitant corticosteroid therapy, and dyslipidemia ▪ Arthopathy ▪ Patients with seizure history ▪ QTc prolongation ▪ Phototoxicity ▪ Patients with myasthenia gravis; may exacerbate symptoms ▪ Patients with glucose 6-phosphate dehydrogenase deficiency		
	▪ Gatifloxacin has been well tolerated. The most common adverse effects include nausea, diarrhea, headache, dizziness, and vaginitis. ▪ Gatifloxacin appears to have a low propensity for phototoxicity or crystalluria	▪ Gemifloxacin has the potential for QT prolongation in some patients, especially those with a history of QT prolongation, hypokalemia or hypomagnesemia, and those receiving class IA or III antiarrhythmic agents. ▪ The most common adverse effects occurring in clinical trials included diarrhea, rash, nausea, and headache. ▪ Gemifloxacin has a low propensity for photosensitivity.	▪ Common side-effects of the oral and intravenous dosage forms include nausea, headache, diarrhea, insomnia, dizziness, and constipation.

Third Generation Quinolones			
Characteristic	**gatifloxacin**	**gemifloxacin**	**levofloxacin**
	Tequin®	Factive®	Levaquin®
Pharmacokinetics issues	▪ Oral gatifloxacin is rapidly absorbed, with peak serum levels occurring in 1 to 2 hours. Metabolism is minimal and the majority of a dose is excreted unchanged in the urine. ▪ The elimination half-life ranges from 7 to 14 hours. ▪ Due to similar pharmacokinetics, the oral and IV routes of administration are considered interchangeable. ▪ Gatifloxacin can be given concurrently with food, including milk and supplements containing calcium. Oral doses of gatifloxacin should be given at least 4 hours before ferrous sulfate, supplements containing zinc, magnesium, or iron, or antacids containing magnesium or aluminum	▪ Gemifloxacin tablets are rapidly absorbed with peak plasma concentrations observed between 0.5 and 2 hours following administration. ▪ Hepatic metabolism is limited, with no important p450 enzyme involvement. ▪ Approximately 61% of a dose is excreted in the feces and remaining drug is excreted renally. The mean half-life at steady-state is approximately 7 hours ▪ Gemifloxacin may be taken without regard to meals	▪ Levofloxacin is essentially completely absorbed after oral administration with peak plasma concentrations attained 1 to 2 hours after the dose. ▪ Levofloxacin does not invert metabolically to its enantiomer, D-ofloxacin, and is excreted primarily unchanged in the urine. ▪ The elimination half-life of levofloxacin is 6 to 8 hours ▪ Oral levofloxacin can be taken without regard to meals
Key Populations	▪ No dosage adjustment is required based on age or gender ▪ Since the majority of a dose is excreted unchanged in the urine, a dosage adjustment is recommended for patients with a ClCr < 40 mL/min, including patients on hemodialysis and on CAPD. The recommended dosage in patients with renal impairment is an initial dose of 400 mg followed by: ➢ =40 mL/min: 400 mg every day ➢ <40 mL/min: 200 mg every day ➢ Hemodialysis 200 mg every day ➢ CAPD 200 mg every day	▪ For patients with a ClCr > 40 mL/min, no dose adjustment is necessary. ▪ For patients with a ClCr = 40 mL/min, the recommended dose is 160 milligrams every 24 hours	▪ There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in ClCr are taken into account ▪ Levofloxacin is mainly excreted as unchanged drug in the urine. To avoid drug accumulation, dosage adjustments are necessary in patients with ClCr <50 mL/min. ▪ In the treatment of acute bacterial exacerbation, chronic bronchitis, community acquired pneumonia, acute maxillary sinusitis, chronic prostatitis, uncomplicated skin and skin structure infection, the recommended dosage for patients with impaired renal function is a initial dose of 500 mg followed by:

Third Generation Quinolones			
Characteristic	**gatifloxacin**	**gemifloxacin**	**levofloxacin**
	Tequin®	Factive®	Levaquin®
			➢ ClCr 20-49: 250 mg every 24 hours ➢ ClCr 10-19: 250 mg every 48 hours ➢ Hemodialysis: 250 mg every 48 hours ➢ CAPD: 250 mg every 48 hours

Third Generation Quinolones				
Characteristic	**lomefloxacin**	**moxifloxacin**	**sparfloxacin**	trovafloxacin
	Maxaquin®	Avelox®	Zagam®	Trovan
Pharmacology	• Quinolones affect bacterial cells by interfering with DNA and the enzyme DNA gyrase (topoisomerase II). The formation of the quinolone-gyrase-DNA complex prevents the DNA polymerase from proceeding at the replication fork, thus stopping DNA synthesis			
	• Lomefloxacin is a third-generation quinolone with a 3-piperazine moiety, structurally similar to other quinolones such as enoxacin, ciprofloxacin, and norfloxacin. • The extra fluorine on the quinolone nucleus separates this compound from the second generation quinolones (ciprofloxacin and norfloxacin). It also makes lomefloxacin more metabolically stable. • It has a spectrum of activity similar to other quinolones (Wise et al, 1988).	• Moxifloxacin is a fluoroquinolone with a broad spectrum of antimicrobial activity, including gram-positive and gram-negative organisms, Chlamydia spp, anaerobes, and Mycobacterium tuberculosis. Similar to trovafloxacin, grepafloxacin, and sparfloxacin, the activity of moxifloxacin against gram-positive pathogens is improved relative to conventional fluoroquinolones • There is some in vitro evidence that resistance to moxifloxacin in gram-positive bacteria occurs more slowly and is less frequent compared to other fluoroquinolones, including trovafloxacin and grepafloxacin	Withdrawn from market due to commercial reasons in 2001	Restricted for use in inpatient faculties for patients with serious life-threatening infections. Has been associated with serious liver injury resulting in liver transplantation or death
Date of FDA Approval	Feb 1992	Dec 1999		
Generic available?	No	No		
Patient Expiration (if single source)	Feb 2006			
Manufacturer (if single source)	Pharmacia	Bayer		
Dosage forms / route of admin	Tablet 400 mg	Tablet 400 mg IV (not in PDL)		
Dosing frequency	Once daily	Once daily		

Third Generation Quinolones				
Characteristic	**lomefloxacin**	**moxifloxacin**	**sparfloxacin**	trovafloxacin
	Maxaquin®	Avelox®	Zagam®	Trovan
General dosing guidelines	▪ Usual oral adult dose: 400 mg daily for 3 to 14 days, depending on the organism and site of infection. ▪ The dose for prevention of urinary tract infections after transurethral surgery or transrectal prostate biopsies is 400 mg one time, 1 to 6 hours prior to the procedure.	▪ Respiratory tract infections (including sinusitis, chronic bronchitis, and CAP):, 400 mg PO/IV once daily for 5 to 14 days, ▪ Uncomplicated skin and skin structure infections: 400 mg PO/IV once daily for 7 days		
Pediatric Labeling	▪ The safety and efficacy in children and adolescents less than 18 years of age have not been fully established			
FDA Labeled Indications	▪ Susceptible infections due to H. influenzae, M. catarrhalis, E. coli, K. pneumoniae, P. mirabilis, S. saprophyticus, P. aeruginosa ▪ Chronic bronchitis, acute bacterial exacerbation ▪ Urinary tract infections, complicated and uncomplicated ▪ Urinary tract infection prophylaxis, transurethral surgery and transrectal prostate biopsy	▪ chronic bronchitis ▪ community-acquired pneumonia ▪ conjunctivitis ▪ sinusitis ▪ skin and skin structure infection		
Other Studied Uses		tuberculosis		
Contraindications	Hypersensitivity to any fluoroquinolones			
Drug interactions	▪ Decreased GI absorption: sucralfate, iron salts, didanosine, antacids ▪ Theophylline ▪ Cimetidine ▪ Anticoagulants ▪ NSAIDs			
	▪ Probenecid	▪ antiarrhythmic agents		

Third Generation Quinolones				
Characteristic	**lomefloxacin**	**moxifloxacin**	**sparfloxacin**	trovafloxacin
	Maxaquin®	Avelox®	Zagam®	Trovan
Major AEs / Warnings	▪ associated with phototoxicity; avoid direct and indirect sunlight while on therapy and several days after therapy ▪ known or suspected CNS disorders; may predispose to seizures or lowering seizure threshold; lomefloxacin associated with increased risk for seizures when compared to other quinolones ▪ safety and efficacy have not been established for the treatment of acute exacerbation of chronic bronchitis caused by S. pneumoniae; should not be used if S. pneumoniae is the suspected organism ▪ safety and efficacy have not been established for the treatment of P. aeruginosa bacteremia ▪ neurotoxicity; risk factors include renal failure, underlying CNS disease, and increased CNS penetration of the drug ▪ tendonitis; risk factors include patients over 60 years of age, renal failure, dialysis, concomitant corticosteroid therapy, and dyslipidemia			
	▪ The most frequent adverse effects are headaches, nausea, and abdominal pain. Moderate to severe phototoxicity has been reported. ▪ Patients with chronic bronchitis and suspected S. pneumoniae infection should not receive lomefloxacin ▪ Caution should be used in persons with history of epilepsy, psychosis, or increased intracranial pressure.	▪ Nausea and diarrhea are the most common adverse effects of oral therapy. ▪ Moxifloxacin should be avoided in patients with prolongation of the QT interval		
Pharmacokinetics issues	▪ Lomefloxacin is well-absorbed after oral administration. ▪ Lomefloxacin is 20% protein bound; the volume of distribution is 1.8 to 2.5 L/kg. ▪ Lomefloxacin is excreted primarily unchanged in the urine; its elimination half-life ranges from 6.4 to 8.19 hours. ▪ Food prolongs the time to peak plasma concentration of lomefloxacin but does not decrease the peak concentration in plasma or AUC. May be taken with or without food	▪ The oral bioavailability of moxifloxacin is approximately 90%; after usual therapeutic doses (400 mg), peak plasma levels occur in 1.5 hour. ▪ Moxifloxacin is metabolized in the liver and excreted in urine (20% unchanged) and bile; metabolites do not appear active. The elimination half-life is about 13 hours. ▪ May be taken without regard to meals. administered concomitantly with food		

Third Generation Quinolones				
Characteristic	**lomefloxacin**	**moxifloxacin**	**sparfloxacin**	trovafloxacin
	Maxaquin®	Avelox®	Zagam®	Trovan
Key Populations	▪ FDA Pregnancy Category C ▪ Some animal reproductive studies (rats) have demonstrated that lomefloxacin at 32 times the human dose (based on mg/kg) did not impair fertility or cause harm to the fetus. However, using monkey or rabbit models, lomefloxacin did demonstrate teratogenetic effects between 2 to 12 times the human dose (based on mg/kg) ▪ No dosage adjustment is necessary for elderly patients with normal renal function (ClCr = 40 mL/min/1.73 m2 ▪ Because lomefloxacin is renally eliminated, and the elderly may have impaired renal function, the risk of toxic reactions may be greater in this population. ▪ ClCr 10-40 40 mL/min/1.73 m2: initial oral loading dose of 400 mg is followed by 200 mg once daily for the duration of therapy	▪ FDA Pregnancy Category C ▪ No dosage adjustment is required based on age or renal function		
	▪ There is no clinical evidence to suggest greater efficacy of any one of gatifloxacin, levofloxacin, or moxifloxacin for respiratory tract infections. ▪ Levofloxacin, moxifloxacin, and gatifloxacin have all been associated with QTc prolongation. Several authors have suggested the risk of QTc prolongation and torsades de points is small, and can be minimized by avoiding use in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA or class III antiarrhythmics.[18,123,124] ▪ Ciprofloxacin: Only fluoroquinolone available as a suspension. Previously, ciprofloxacin was the most active fluoroquinolone against P. aeruginosa. Recent in vitro evidence suggests levofloxacin and gatifloxacin are as active against P. aeruginosa as ciprofloxacin. ▪ Levofloxacin: The l-isomer of ofloxacin. In comparison to ofloxacin, levofloxacin has fewer CNS side effects, a longer half-life (once daily dosing), extended spectrum of activity, and twice the potency. For most bacteria, the MIC values for levofloxacin are half those of ofloxacin. There have been case reports of levofloxacin failure in patients with pneumococcal respiratory tract infections.125,126. Levofloxacin is the only fluoroquinolone FDA approved for the treatment of respiratory tract infections due to penicillin-resistant S. pneumoniae. ▪ Moxifloxacin: The most potent fluoroquinolone in vitro against S. pneumoniae. Moxifloxacin is available only in oral formulation as a tablet. ▪ Gatifloxacin: Blood glucose should be closely monitored in patients with diabetes taking gatifloxacin. In the first 3 days of therapy, patients may be especially at risk for hypoglycemia; after 3 days, the risk of hyperglycemia may be increased.		

References

6. Electronic Orange Book: http://www.fda.gov/cder/ob/default.htm
7. Selevan J, Cada D eds. The Formulary Monograph Service. http://www.formularymonographs.com/default.asp
8. Pharmacy Benefits Management Strategic Healthcare Group, Department of Veterans Affairs. http://www.vapbm.org/PBM/menu.asp
9. Hutchison TA & Shahan DR (Eds): DRUGDEX® System. MICROMEDEX, Greenwood Village, Colorado (Edition expires 12/2003)
10. Electronic Orange Book: http://www.fda.gov/cder/ob/default.htm
11. Selevan J, Cada D eds. The Formulary Monograph Service. http://www.formularymonographs.com/default.asp
12. Pharmacy Benefits Management Strategic Healthcare Group, Department of Veterans Affairs. http://www.vapbm.org/PBM/menu.asp
13. Hutchison TA & Shahan DR (Eds): DRUGDEX® System. MICROMEDEX, Greenwood Village, Colorado (Edition expires 12/2003)

Second Generation Cephalosporins			
Characteristic	**Cefaclor**	**Cefprozil**	**Cefuroxime**
	Ceclor®, Ceclor® CD	Cefzil®	Ceftin®
Pharmacology	Second-generation oral cephalosporins, like other beta-lactam antibiotics, inhibit bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs). They inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. It is thought that the beta-lactam antibiotics inactivate transpeptidase via acylation of the enzyme with cleavage of the CO-N bond of the beta-lactam ring. Upon exposure to beta-lactam antibiotics, bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.		
Date of FDA Approval	Before Jan 1982	Dec 1991	Dec 1987
Generic available?	Yes	No	Yes
Patent Expiration (if single source)		There are no unexpired patents for this product in the Orange Book Database	
Manufacturer (if single source)		Bristol-Myers Squibb	
Dosage forms / route of admin	Capsules Extended release tablet Oral suspension	Tablets Oral suspension	Tablets Oral suspension
Dosing frequency	Q 8 hours Q 12 hours (CD)	BID – once daily	BID
General dosing guidelines	Usual doses for the suspension or capsules are 250 mg every 8 hours, with 500 mg every 8 hours suggested in severe infections. For the extended release tablets, 375 mg to 500 mg every 12 hours are suggested. The extended release form should be taken with food. Dosage reductions are not necessary in renal failure.	The normal adult dose of cefprozil is 250 to 500 mg orally every 12 to 24 hours for 10 days, depending on the organism and on the site and severity of infection. In children, the usual oral dose is 15 to 30 mg/kg/day for 10 days.	Oral cefuroxime axetil is administered as 250 mg orally twice a day for most indications. For pediatric patients who can swallow tablets whole, the usual dose is 125 mg to 250 mg orally twice daily for 10 days. For pediatric patients (3 months to 12 years) the usual dose is 20 to 30 mg/kilogram/day in 2 divided doses for a duration of 10 days.

Second Generation Cephalosporins			
Characteristic	**Cefaclor**	**Cefprozil**	**Cefuroxime**
	Ceclor®, Ceclor® CD	Cefzil®	Ceftin®
Pediatric Labeling	Yes	Yes	Yes
FDA Labeled Indications	otitis media respiratory tract infections skin and skin-structure infections urinary tract infections	acute otitis media bronchitis chronic bronchitis lower respiratory tract infections otitis media pharyngitis pneumonia sinusitis skin infections tonsillitis upper respiratory tract infections	▪ bone and joint infections ▪ bronchitis ▪ gonorrhea ▪ lyme disease ▪ meningitis ▪ otitis media ▪ pharyngitis/tonsillitis ▪ respiratory tract infections - lower ▪ sinusitis ▪ skin and soft tissue infections ▪ surgical prophylaxis - general ▪ surgical prophylaxis - gynecologic surgery ▪ urinary tract infections
Other Studied Uses	gonorrhea sinusitis	osteomyelitis	Juvenile discitis Pneumonia-nosocomial (prophylaxis) Surgical prophylaxis – cardiac, thoracic
Contraindications	Known allergy to the cephalosporin group of antibiotics		
Drug interactions	▪ May potentiate the nephrotoxicity of aminoglycosides ▪ Tetracycline derivatives may impair bactericidal effects of cephalosporins. ▪ Probenecid inhibits renal excretion		
Major AEs / Warnings	Hypersensitivity reactions are possible and may require epinephrine and other emergency measures Use with caution in patients with a history of hypersensitivity to penicillins Pseudomembranous colitis should be considered in patients developing diarrhea while being treated		

Second Generation Cephalosporins			
Characteristic	**Cefaclor**	**Cefprozil**	**Cefuroxime**
	Ceclor®, Ceclor® CD	Cefzil®	Ceftin®
Major AEs / Warnings (cont)	▪ Primary toxic effects are nausea and diarrhea; ▪ CNS reactions (headache, lassitude) have occurred rarely, as have elevations in hepatic-function tests and cholestatic jaundice ▪ Skin reactions have been reported, including hypersensitivity reactions and a serum-sickness like reaction.	▪ Headache, nausea, vomiting, abdominal pain, and diarrhea have occurred	▪ Cefuroxime and cefuroxime axetil are relatively safe and have been associated with few serious adverse effects. ▪ Gastrointestinal effects are the most common adverse effects reported with cefuroxime axetil. ▪ Blood dyscrasias (eosinophilia, neutropenia, and leukopenia) have been associated with cefuroxime sodium therapy
Pharmacokinetics issues	Cefaclor is well-absorbed following oral administration, with peak serum levels occurring in 1 hour Most of a dose (80%) is excreted unchanged in the urine; Half-life of 0.5 to 1 hour.	▪ Cefprozil is rapidly absorbed, with peak plasma levels occurring 1 to 2 hours after oral administration ▪ Eliminated largely unchanged in the urine; ▪ Elimination half-life is approximately 1 to 2 hours.	▪ Cefuroxime is widely distributed to most body fluids and tissues, including cerebrospinal fluid. Among second generation cephalosporins, cefuroxime is the only agent to achieve therapeutic levels in the cerebrospinal fluid. ▪ The half-life of cefuroxime is about 1.1 to 1.4 hours. ▪ Cefuroxime is only minimally metabolized, with greater than 95% of the dose being excreted unchanged in the urine following intravenous administration. ▪ Cefuroxime axetil is a prodrug which is converted in vivo to the active drug cefuroxime.
Key Populations	▪ Dosage adjustment is not necessary in elderly subjects with normal serum creatinine values ▪ Pregnancy Category B		

Second Generation Cephalosporins			
Characteristic	**Cefaclor**	**Cefprozil**	**Cefuroxime**
	Ceclor®, Ceclor® CD	Cefzil®	Ceftin®
Renal Impairment	▪ Cefaclor should be administered with caution in the presence of seriously impaired renal function. Since the half-life of cefaclor in anuria is 2.3 to 2.8 hours, dosage adjustments for patients with moderate or severe renal impairment are not usually required. ▪ The following dosage adjustments in patients with renal dysfunction are recommended: ClCr 10 to 50 mL/min, 50% to 100% of the normal dose; ClCr <10, 50% of the normal dose	▪ The manufacturer of CEFPROZIL recommends a 50% reduction in dosage in patients with a ClCr <30 mL/min; however, the dosing interval should remain unchanged	The following dosage reduction in patients with renal failure is recommended: ▪ ClCr >50 mL/min: 45% to 100% of the usual dose in patients with mild renal failure ▪ ClCr 10-50 mL/min: 10% to 45% of the usual dose in patients with moderate renal failure ▪ ClCr <10 mL/min 5% to 10% of the usual dose in patients with severe renal failure
Notes	Cefaclor is an oral semisynthetic cephalosporin that is classified as a second-generation agent but has an in vitro spectrum of activity similar to the oral first-generation cephalosporins with the exception of having activity against H influenzae and B catarrhalis. The primary place in therapy of cefaclor is in treating acute otitis media and acute sinusitis caused by H influenzae or B catarrhalis that is resistant to amoxicillin, the preferred drug of choice.	Cefprozil is a broad-spectrum cephalosporin with a spectrum of activity similar to that of cefaclor. Other than a relatively long serum half-life, cefprozil offers no particular advantage over other similar agents. It is effective in treating various types of upper- and lower-respiratory tract infections, including pharyngitis/tonsilitis, otitis media, acute sinusitis, and acute bronchitis, as well as uncomplicated skin and skin-structure infections	Although cefuroxime axetil offers the advantage of twice daily dosing due to its relatively long half-life, its place in therapy with regard to other antibiotics appears to be limited at present. The drug has been similarly as effective as cefaclor, amoxicillin/clavulanic acid and cephalexin in the treatment of uncomplicated UTIs; however, other less expensive agents are also effective.

Third Generation Cephalosporins					
Characteristic	**Cefdinir**	**Cefixime**	**Cefpodoxime**	**Ceftibuten**	**Cefditoren**
	Omnicef®	Suprax®	Vantin®	Cedax®	Spectracef®
Pharmacology	Third-generation oral cephalosporins, like other beta-lactam antibiotics, inhibit bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs). They inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. It is thought that the beta-lactam antibiotics inactivate transpeptidase via acylation of the enzyme with cleavage of the CO-N bond of the beta-lactam ring. Upon exposure to beta-lactam antibiotics, bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.				
Date of FDA Approval	Dec 1997	In July 2002, Wyeth discontinued manufacturing cefixime. Tablet inventory was depleted in 10/2002, and suspension inventory is expected to be depleted by 3/2003	Aug 1992	Dec 1995	Aug 2001
Generic available?	No		No		
Patent Expiration (if single source)	There are no unexpired patents for this product in the Orange Book Database		There are no unexpired patents for this product in the Orange Book Database	There are no unexpired patents for this product in the Orange Book Database	Oct 2016
Manufacturer (if single source)	Abbott		Pharmacia and Upjohn	Biovail	Purdue Pharma
Dosage forms / route of admin	Capsules: 300mg Suspension: 125mg/5ml.		Capsule: 400mg, Suspension: 90, 180 mg/5mL	Tablet: 200mg & 400mg Suspension: 100mg/5ml	Tablet: 200 mg
Dosing frequency	Once daily - BID		BID	Once daily - BID	BID
General dosing guidelines	The usual oral dose of cefdinir in adults and adolescents is 300 mg orally twice daily. An oral dose of 600 mg once daily has been used in streptococcal pharyngitis. In otitis media with effusion in children, doses of either 7 mg/kg orally twice daily or		The recommended adult dosage is 100 to 400 mg twice daily for up to 14 days depending on the severity of infection. The usual pediatric dosage is 5 mg/kg twice daily for up to 10 days depending on the infection.	In adults, the usual dose is 400 mg daily for 10 days. In children a dose of 9 mg/kg/day for 10 days has been administered.	In adults and adolescents (12 years and older) for the treatment of CAD and acute exacerbation of chronic bronchitis dose is 400 mg BID for 14 and 10 days, respectively. The dose for the treatment of pharyngitis/ tonsillitis and

Third Generation Cephalosporins					
Characteristic	**Cefdinir**	**Cefixime**	**Cefpodoxime**	**Ceftibuten**	**Cefditoren**
	Omnicef®	Suprax®	Vantin®	Cedax®	Spectracef®
General dosing guidelines (cont)	14 mg/kg orally once daily have been administered. A strawberry-flavored suspension is available for children.				uncomplicated skin and skin structure infections is 200 mg BID for 10 days. Should be taken with meals.
Pediatric Labeling	Yes		Yes	Yes	Safety and efficacy have not been established in children younger than 12 years of age. Adolescents 12 years of age and older should receive the usual adult dose
FDA Labeled Indications	Acute bacterial otitis media Bronchitis - chronic Community-acquired pneumonia Middle ear infections Otitis media Pharyngitis - tonsillitis - streptococcal Pneumonia Sinusitis Skin infections Skin structure Strep throat Streptococcal pharyngitis		Acute maxillary sinusitis Bronchitis Gonorrhea Otitis media Pharyngitis Pneumonia Respiratory infections - lower Respiratory infections - upper Skin and skin structure infections Tonsillitis Urinary tract infections	▪ Acute Otitis Media ▪ Pharyngitis/ Tonsillitis ▪ Acute Exacerbations of Chronic Bronchitis	▪ Acute bacterial exacerbation of chronic ▪ AECB ▪ Cellulitis ▪ Community-acquired pneumonia ▪ Furunculosis ▪ Impetigo ▪ Lower respiratory tract infections ▪ Pharyngitis ▪ Skin/skin structure infections ▪ Tonsillitis

Third Generation Cephalosporins					
Characteristic	**Cefdinir**	**Cefixime**	**Cefpodoxime**	**Ceftibuten**	**Cefditoren**
	Omnicef®	Suprax®	Vantin®	Cedax®	Spectracef®
Other Studied Uses	vaginitis		cystic fibrosis	Enteric infections Gynecologic infections Lower respiratory tract infections Gonococcal urethritis Complicated UTI	Otitis media UTI
Contraindications	Known allergy to the cephalosporin group of antibiotics				
					Carnitine deficiency
Drug interactions	▪ May potentiate the nephrotoxicity of aminoglycosides ▪ May increase anticoagulants hypoprothrombinemic effects. ▪ Tetracycline derivatives may impair bactericidal effects of cephalosporins. ▪ Cephalosporins may have a delayed onset drug interaction with heparin.				
	▪ Iron supplements, antacids reduce absorption. ▪ Probenecid inhibits renal excretion.				
Major AEs / Warnings	Hypersensitivity reactions are possible and may require epinephrine and other emergency measures Renal impairment; the total daily dose should be reduced Use with caution in patients with a history of hypersensitivity to penicillins Pseudomembranous colitis should be considered in patients developing diarrhea while being treated				

Third Generation Cephalosporins					
Characteristic	**Cefdinir**	**Cefixime**	**Cefpodoxime**	**Ceftibuten**	**Cefditoren**
	Omnicef®	Suprax®	Vantin®	Cedax®	Spectracef®
Major AEs / Warnings (cont)	Diarrhea is a frequent adverse effect of cefdinir (up to 19% of patients) Eosinophilia and abnormal liver function tests have been reported with higher than usual doses. Ferrous salts reduce the bioavailability of cefdinir.		▪ Eosinophilia has occurred during cefpodoxime therapy; headaches and asthenia have been reported in isolated instances. ▪ Diarrhea, abdominal pain, and nausea and vomiting have also occurred. ▪ Candidial vaginitis has been reported with cefpodoxime therapy. ▪ Urticaria, skin eruptions, and dermal mycoses have occurred.	▪ Gastrointestinal disturbances may occur, including nausea, vomiting, diarrhea, and heartburn. ▪ Elevations in liver function tests have also occurred.	Nausea, diarrhea, abdominal pain, headache, eosinophilia, vaginal moniliasis, elevation of liver enzymes, and rash have been reported.
Pharmacokinetics issues	Cefdinir is slowly absorbed after oral doses, with peak serum levels occurring within 4 hours. Serum levels of 0.7 to 1.7 mcg/mL are observed with 200-mg oral doses, declining to 0.1 mcg/mL or less by 12 hours. Cefdinir is excreted in the urine and has an elimination half-life of 1 to 4 hours.		▪ Oral cefpodoxime is a prodrug, administered as the proxetil ester, which is absorbed and rapidly hydrolyzed to active CEFPODOXIME in the gut ▪ Peak plasma concentrations are reached 2 to 3 hours after oral administration. ▪ Half-life is approximately 2.5 hours in patients with normal renal function. ▪ It is excreted primarily as unchanged drug in the urine. ▪ Take tablets with food ▪ Take suspension, with or without food	▪ Ceftibuten is rapidly absorbed, producing peak serum levels 2 to 3 hours after oral administration. ▪ The drug penetrates well into inflammatory fluid, with concentrations approximating those in the serum. ▪ Ceftibuten is excreted primarily unchanged in the urine with an elimination half-life of approximately 2 hours	▪ Cefditoren pivoxil is a prodrug, and is hydrolyzed in the intestinal wall to cefditoren; ▪ Peak cefditoren plasma levels occur in 1.5 to 3 hours. ▪ Cefditoren is mainly eliminated by the kidneys. The elimination half-life of cefditoren is 1 to 2 hours.

Third Generation Cephalosporins					
Characteristic	**Cefdinir**	**Cefixime**	**Cefpodoxime**	**Ceftibuten**	**Cefditoren**
	Omnicef®	Suprax®	Vantin®	Cedax®	Spectracef®
Special Populations	Pregnancy Category B		▪ Dosage adjustment of cefpodoxime is not necessary in healthy geriatric patients		
			Pregnancy Category B		
Renal Impairment	A dose of cefdinir 300 mg once daily is recommended for adult patients with ClCr <30 mL/min		▪ In patients with severe renal impairment (ClCr <30 mL/min) the dosing interval for cefpodoxime should be increased to every 24 hours	▪ No dosage adjustments are necessary for patients with ClCr = 50 mL/min ▪ For patients with a ClCr of 30 to 49 mL/min a rec. dose is 200 mg daily. ▪ For patients with a ClCr 5 to 29 mL/min, rec dose is 100 mg daily	▪ For patients with a ClCr between 30 to 49 mL/min/1.73 m^2, the dose of cefditoren should not be more than 200 mg BID ▪ For patients with a Clcr less than 30 mL/min/1.73 m^2t, the dose should be reduced to 200 mg every day
	▪ In general, and with some notable exceptions, 3rd generation cephalosporins have potent activity against *S. pneumoniae* (including some strains with elevated penicillin MIC), *S. aureus, H. influenzae, M. catarrhalis, Neisseria* spp., *E. coli, Klebsiella pneumoniae,* and *P. mirabilis.* ▪ 3rd generation cephalosporins are not effective against methicillin-resistant *S. aureus* or highly resistant penicillin-resistant *S. pneumoniae* ▪ Cefixime and cefpodoxime are slowly absorbed and reach lower maximal serum concentrations relative to the other orally administered 3rd generation cephalosporins. ▪ This category is the most resistant to β-lactamase produced by gram-negative organisms. ▪ Do attain higher concentrations in the cerebrospinal fluid than other cephalosporins. ▪ Oral third generation agents are active against the pathogens responsible for acute otitis media, but GI side effects and higher cost limit their usefulness. ▪ Active against most clinically important *Enterobacteriaceae* and have been used to treat uncomplicated urinary tract infection, however, they offer no advantage over equally effective, less expensive agents. ▪ Cefdinir oral suspension is preferred over several other antibiotic suspensions, due to improved palatability. Overall taste ranking of antibiotics, from highest to lowest, was loracarbef > cefdinir > azithromycin > ciprofloxacin > TMP-SMX > clarithromycin > trimethoprim > amoxicillin/clavulanate > cefpodoxime > cefuroxime. ▪ Cefpodoxime: Has activity against *S. aureus*.[9] ▪ Cefditoren: Only indicated for adults and adolescents. Decreases serum concentration of carnitine, the clinical significance of which in normal patients is unclear. Tablets are formulated with a milk protein and should not be given to patients with a milk protein hypersensitivity. ▪ Ceftibuten: Does not have activity against *S. aureus*.				

References

1. Steele RW et al. Compliance issues related to the selection of antibiotic suspensions for children. *Pediatr Infect Dis J* 2001;20:1-5.
2. Powers JL et al. Comparison of the palatability of the oral suspension of cefdinir vs. amoxicillin/clavulanate potassium, cefprozil, and azithromycin in pediatric patients. *Pediatr Infect Dis J* 2000;19:S174-80.
3. Anonymous. Cefditoren (Spectracef)—A new oral cephalosporin. *The Medical Letter on Drugs and Therapeutics* 2002;44(1122):5-6.
4. Bergan T. Pharmacokinetic properties of the cephalosporins. *Drugs* 1987:34:Suppl. 2:89-104. Finch R. Treatment of respiratory tract infections with cephalosporin antibiotics. *Drugs* 1987;34:Suppl. 2:180-204.
5. Nassar WY, Allen BM. A double-blind comparative clinical trial of cephalexin and ampicillin in the treatment of childhood acute otitis media. Curr Med Research and Opinion 1974;2(4)34-6.
6. "Orange Book": http://www.fda.gov/cder/ob/default.htm
7. Hutchison TA & Shahan DR (Eds): DRUGDEX® System. MICROMEDEX, Greenwood Village, Colorado (Edition expires 12/2003)
8. Steele RW et al. Compliance issues related to the selection of antibiotic suspensions for children. *Pediatr Infect Dis J* 2001;20:1-5.
9. Powers JL et al. Comparison of the palatability of the oral suspension of cefdinir vs. amoxicillin/clavulanate potassium, cefprozil, and azithromycin in pediatric patients. *Pediatr Infect Dis J* 2000;19:S174-80.
10. Bergan T. Pharmacokinetic properties of the cephalosporins. *Drugs* 1987:34:Suppl. 2:89-104. Finch R. Treatment of respiratory tract infections with cephalosporin antibiotics. *Drugs* 1987;34:Suppl. 2:180-204.
11. Electronic Orange Book: http://www.fda.gov/cder/ob/default.htm
12. Selevan J, Cada D eds. The Formulary Monograph Service. http://www.formularymonographs.com/default.asp
13. Pharmacy Benefits Management Strategic Healthcare Group, Department of Veterans Affairs. http://www.vapbm.org/PBM/menu.asp
14. Hutchison TA & Shahan DR (Eds): DRUGDEX® System. MICROMEDEX, Greenwood Village, Colorado (Edition expires 12/2003)